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In re Lamotrigine 50 milligram
And 250 milligram oral tablets

CITIZEN'S PETITION
RE-LISTING PETITION

This is a RE-LISTING PETITION submitted pursuant to 21 U.S.C. § 505(j)(2)(C) and 21 C.F.R. § 10.30.

Action Requested

The Commissioner of the Food & Drug Administration previously approved the reference listed drug in six different strengths, including 50 mg and 250 mg. These two strengths have since been withdrawn from the market. This requests the Commissioner make a determination that these two strengths were not withdrawn due to safety nor efficacy concerns.

This Petition therefore requests the Commissioner of the Food & Drug Administration make a determination that:

A. the drug product lamotrigine oral tablets, in the strength of 50 mg is suitable for consideration in an Abbreviated New Drug Application; and

B. the drug product lamotrigine oral tablets, in the strength of 250 mg is suitable for consideration in an Abbreviated New Drug Application.

2005P-0237

CP1

Statement of Grounds for Relief

The Reference Listed Drug

The reference listed drug product is Lamictal® brand lamotrigine oral tablets. The reference listed drug is an antiepileptic drug. *See* FDA approved labeling text for Lamictal® brand lamotrigine tablets and (NDA 20-241/S-017) (20 June 2003) at page 2, line 56 (copy enclosed). The reference listed drug is the subject of approved New Drug Application No. 20-241. The Holder is GlaxoSmithKline.

The NDA approval for the reference listed drug has not been withdrawn due to safety nor efficacy concerns. To the contrary, it was approved for use on 27 December 1994, and since that time has enjoyed a record of safety and effectiveness which supported its approval for additional labeled indications. *See* Paul Leber, Letter (14 Dec. 1998) (copy enclosed); Russell Katz, Letter (14 Jan 2004) (copy enclosed). It is currently approved for use as adjunctive therapy for partial seizures in adults and pediatric patients at least two years of age. *Id.* at page 13, lines 368 *et seq*. It is also approved for use as mono-therapy in adults, and for bipolar disorder maintenance. *Id.*

The approved dosing regimen requires that the drug dosage be adjusted to the patient's body weight. For example, epilepsy patients 2 to 12 years of age using valproate combination therapy require an initial daily dose of 0.15 mg per kilogram of patient body weight. *Id.* at page 38, Table 9. After two weeks, the recommended dosage increases to 0.3 mg per kilogram of body weight. *Id.* After four weeks, the recommended dosage increases to 1.0 to 5.0 mg per kilogram of body weight. *Id.*

Similarly, the approved dosages for bipolar patients not taking valproate range from a relatively low initial dose of 50 mg per day, and gradually increasing to a maintenance dose of up to 400 mg per day. *Id.* at page 41.

Similarly, to minimize adverse side effects, discontinuing use of this drug requires gradually reducing the dosage over time. *See id.*

Because the dosage must be adjusted over time, and must be adjusted to respond to the patient's body weight, the reference listed drug is currently available in four dosage strengths: 25 mg, 100 mg, 150 mg and 200 mg. *See* United States Food & Drug Administration, Electronic Orange Book entry for Lamictal® brand lamotrigine oral tablets (20 May 2005) (copy attached).

In addition to these four strengths, two additional strengths – 50 mg and 250 mg – were approved by the Agency. These two strengths were subsequently withdrawn from the market.

The Proposed Re-Listed Dosage Strength

An Abbreviated New Drug Application may be filed for the approval of a new drug product that is the same as the reference listed drug. 21 U.S.C.A.§ 355(j)(2)(A) (2005). An Abbreviated New Drug Application may also be filed for a new drug product which is the same as the reference listed drug except for a difference in dosage strength, if the Commissioner grants permission to file such an Application by making an administrative finding that the difference in dosage form is suitable. See 21 U.S.C.A. § 355(j)(2)(C) (2005); 21 C.F.R. § 314.93(b). The Commissioner has authority to approve a Citizen's Petition seeking a re-listing of a discontinued dosage strength. *See* 21 C.F.R. § 10.25, 10.30 (2005).

Petitioner respectfully requests the Commissioner make a determination that lamotrigine oral tablet drug product is suitable for consideration in an Abbreviated New Drug Application, in the previously-approved strengths of 50 mg and 250 mg

because these two strengths were not withdrawn from the market due to safety nor efficacy concerns.

There is no reason to question the safety and effectiveness of the proposed drug products for their labeled uses. The reference listed drug was approved for use on 27 December 1994. Since that time, it has enjoyed a record of safety and effectiveness which supported its approval for additional labeled indications. *See* Paul Leber, Letter (14 Dec. 1998) (copy enclosed); Russell Katz, Letter (14 Jan 2004) (copy enclosed).

These proposed drug products will contain the same active drug substance as the reference listed drug, have the same route of administration (oral) as the reference listed drug, will have the same delivery mechanism (immediate release), and have the same dosage form (tablet). The labeling of the proposed drug product will also be the same as the currently-approved labeling for the reference listed drug, except for changes which are required because of the difference in manufacturer and the difference in dosage form proposed under this Petition. The proposed products will differ from the reference listed drug only in their dosage strength.

Petitioner believes this re-listing of a previously-approved dosage strength will reduce patient error by improving the ability of clinicians to prescribe precise amounts of the drug substance, and thereby reduce patient compliance error. This would appear especially important where, as here, the patient suffers from a neurological disorder which may impair the patient's ability to follow a complex dosing regimen. For example, asking a patient to take one 50 mg tablet appears less prone to error than asking the same patient to take two 25 mg tablets. Similarly, asking a patient to take one 250 mg tablet appears less prone to error than asking the same patient to take one 200 mg tablet and two

25 mg tablets; it does not appear overly difficult to imagine the patient mistakenly taking two 200 mg tablets and one 25 mg tablet, for an overdose of 425 mg, rather than the 250 mg intended.

Suitability of the 50 mg strength is respectfully believed warranted because the Food & Drug Administration routinely approves Re-Listing Petitions asking for a re-listing of a previously approved dosage strength, where the previously approved strength was not withdrawn from the market due to safety or efficacy concerns.

Suitability of the 250 mg strength is also respectfully believed warranted because the 250 mg strength, while larger than the currently approved 200 mg strength, remains within the range of dosages recommended in the approved labeling. The approved labeling recommends dosages up to 400 mg per day. *See* FDA approved labeling text for Lamictal® brand lamotrigine tablets and (NDA 20-241/S-017 (20 June 2003) at page 42, Table 14, right-hand column. Thus, the proposed 250 mg strength is well within the range of currently-approved dosages.

The record of this product before the Food & Drug Administration includes a problem with prescription-fulfillment. Specifically, in 2000, the Holder issued "Dear Doctor" and "Dear Pharmacist" letters, warning of potential confusion between the trademark for the reference listed drug - Lamictal® - and the trademark Lamisil®, used for an unrelated antifungal drug. *See* N. Scott Sykes, Letter (6 June 2000); N. Scott Sykes, Letter (July 2000); Richard S. Kent, Letter (August, 2000) (copies enclosed).

Petitioner respectfully notes that the proposed products are generic forms of the reference listed drug. These generic products will therefore not carry the potentially-confusing Lamictal® trademark. Therefore, the proposed generic products thus appear safer in this regard than the reference listed drug. There thus appears no reason to question the safety and efficacy of these products.

For the foregoing reasons, Petitioner respectfully believes that the proposed dosages are suitable for approval under an Abbreviated New Drug Application.

Request to Waive Pediatric Assessment

An assessment of the safety and efficacy of the product in pediatric patients is required for any application for a new active ingredient, dosage form, indication, route of administration or dosing regimen. *See* 21 U.S.C. § 355B(A)(4)(ii) (2004).

This Petition does not request any change in active ingredient, dosage form, indication, route of administration, nor dosing regimen. The dosing regimen – the amount of drug the patient will be administered, and when, and for what symptoms, and with what co-administered therapeutics - will remain the same as the dosing regimen currently-approved for the reference listed drug. This Petition proposes changing the strength of the individual tablets, not the drug dosing regimen which those tablets are used for. Petitioner therefore respectfully believes that this Petition does not require pediatric assessment.

In the alternative, Petitioner requests waiver of pediatric assessment, because the Agency has waived and deferred the pediatric assessments for the reference listed drug. *See* Russell KATZ, Letter at page 2 (14 January 2004) ("We are waiving the pediatric study requirement for ages 0 years up to 1 month of age and deferring pediatric studies for ages 1 month to 16 years for" the reference listed drug).

Petitioner therefore respectfully believes that a full waiver of pediatric studies is warranted.

Environmental Impact

Petitioner respectfully believes that it need not submit environmental impact information, because such information is categorically excluded from Citizens Petitions. *See* 21 C.F.R. § 25.31.

Economic Impact

Petitioner respectfully believes that it need not submit economic impact information unless requested to do so by the Commissioner. *See* 21 C.F.R. § 10.30(b).

Action Requested

Petitioner respectfully requests the Commissioner make a determination that:

A. the drug product lamotrigine oral tablets, in the strength of 50 mg is suitable for consideration in an Abbreviated New Drug Application; and

B. the drug product lamotrigine oral tablets, in the strength of 250 mg is suitable for consideration in an Abbreviated New Drug Application.

Petitioner also requests the Commissioner to make a determination that these tablet strengths are either exempt from the requirement for pediatric assessment, or that are subject to assessment and the requirement is waived.

Certification

The undersigned certifies that, to the best of their knowledge and belief, this Suitability Petition includes all information and views upon which the Petition relies, and includes representative data and information known to Petitioner which are unfavorable to this Petition.

Respectfully Submitted,
PHARMACEUTICAL PATENT ATTORNEYS, LLC

By: ______________________________

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Enclosures

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1) Draft "How Supplied" section of product insert for proposed new dosage strength.

2) FDA approved labeling text for Lamictal® brand lamotrigine tablets and (NDA 20-241/S-017 (20 June 2003).

3) FDA ELECTRONIC ORANGE BOOK information for discontinued dosage strengths.

4) Russell Katz, Letter (14 Jan 2004).

5) Paul Leber, Letter (14 Dec. 1998)

6) N. Scott Sykes, Letter (6 June 2000); N. Scott Sykes, Letter (July 2000); Richard S. Kent, Letter (August, 2000).

7) United States Food & Drug Administration, Electronic Orange Book entry for Lamictal® brand lamotrigine oral tablets (20 May 2005).